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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/716,531	Applicant(s) Mahe et al
	Examiner Sheela J. Huff	Group Art Unit 1806

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-15 are pending.

Information Disclosure Statement

2. The IDS filed on 9/19/96 has been made of record and an initialed copy of the PTO-1449 is enclosed.

Specification

3. The disclosure is objected to because of the following informalities:

a. Throughout the specification applicant refers to the tripeptide lysine-proline-valine as LPV (single letter code). The single letter code for lysine is K not L; L=leucine (see Harper's Review of Biochemistry, 20th Ed., p. 17-18 (1985)) . Replacement of L with K is required.

b. In Table IV, it is not clear what the difference between Ac-LPV-NH2 and Ac-L-P-V-NH2 is. These appear to be the same peptide but have different activities.

Appropriate correction is required.

Claim Objections

4. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 refers to all three amino acids in the D-form. However, in claim 1 only pro is present in its D-form because a conventional reading of the tripeptide in claim would clearly indicate that lysine and valine are in their L-form.

Claim Rejections - 35 USC § 112

5. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of tripeptides K(D)PV, does not reasonably provide enablement for peptides that "contain" said tripeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In view of the prior art, Ferreira et al US 5389615 and Oluyomi et al, Eur. J. Pharm. vol. 258 p. 131 (1994), applicant is enabled for the use of a tripeptide to treat inflammation. However, the claims also read on the use of a peptide containing the tripeptide wherein said tripeptide is located anywhere in the peptide. This reads on a peptide **of any length** that has the tripeptide somewhere in it. It is well known that peptides, especially large peptides, have secondary and tertiary structure and therefore conformational structure of the peptide can hide the tripeptide from the surface thereby inactivating the ability of the tripeptide to perform its function. Is there a specific function that would lead one skilled in the art to select the inactive peptides from the

active peptides? If so, then the function should be specifically recited in the body of the claim.

In view of the above, the Examiner believes that undue experimentation would be required by one skilled in the art to use the invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In claim 1, line 5, "existing" should be --exists--. Similar problems are found in claim 3, line 4, claim 4, line 4.

b. In claim 1, line 6, it is unclear if "functional biological equivalent thereof" is referring to the peptide, the tripeptide or the DPro. Also, this terminology renders the claim vague and indefinite. How "functionally equivalent" is equivalent? Applicant attempts to define this terminology on page 3, lines 26+. This definition is also vague. How similar is "similar"? A wherein clause reciting a function would help.

c. In claim 2, the terminology "at the Cterminal end of " renders the claim vague and indefinite. Is applicant referring to the last three amino acids at the C-end or merely a set of three amino acids near the C-end? If applicant is referring to the latter, then how close to the C-end to said amino acids have to be?

d. In claim 5 it is unclear as to where the protecting group is located. Is it on the C-end, the N-end or a side chain?

e. In claims 7-10 it is unclear if the recited concentrations are actually referring to the concentration of the tripeptide in the peptide or the concentration of the peptide.

f. In claims 12-14, it is conventional to refer to a method claim by stating a method not regime.

g. In claims 13-14, lines 3 and 4 respectively, "such" should be --said--.

h. In claim 15, the terminology "derivative thereof" renders the claim vague and indefinite. This terminology is not defined.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferreira et al US 5389615 or Oluyomi et al Eur. J. Pharm. vol. 258 p. 131 (1994).

Ferreira et al disclose the use of a tripeptide K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (inflammation) (col. 2, lines 46-52, lines 59-61, col 3, lines 53-59, col. 4, line 59 to col. 5, line 3, and all the Examples and claims).

Oluyomi et al disclose the use of K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (abstract, p. 134-135 and Tables 2-3).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 4, 7-10 and ~~15~~ 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615 as applied to claims 1-3 and ~~12~~ above.

This reference discloses the use of tripeptides as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (Formula I) where X can be lys or arg and y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys(col. 2, line 22) and Y=valine (col.2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). the preferred form of pro is also D (col. 2, line 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-4.

The only difference between that instant invention is the specific use of Dlys-Dpro-Dval and the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the reference clearly suggests the making and use of Dlys-Dpro-Dval (preferred embodiment). Therefore, in view of this suggestion, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use Dlys-Dpro-Dval to treat pain. The combination of two or more known agents to treat a disease if within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

12. Claims 5-6 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615 as applied to claims 1-3 and 12 above further in view of Lipton US 5157023 and Oluyomi et al Eur. J. Pharm.. vol. 258 p. 131 (1994).

The primary reference discloses the use of tripeptides of IL-1beta as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (Formula I) where X can be lys or arg and y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys(col. 2, line 22) and Y=valine (col.2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). the preferred form of pro is also D (col. 2, line 15-17). These compounds read on the tripeptides and functional equivalents thereof of the instant invention.

The only difference between that instant invention is the use of protecting groups.

Lipton discloses the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active that the unprotected form (col. 4, lines 58-68).

Therefore, in view of the enhanced activity of the protected peptide over the unprotected peptide, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of

the primary and secondary reference are related (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of Il-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related).

13. Claims ~~1-15~~ 1-4, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615 in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Sciences, 16th Ed. (1980), CH 87 and 92 and Oluyomi et al Eur. J. Pharm.. vol. 258 p. 131 (1994).

Ferreira et al discloses the use of tripeptides of IL-1beta as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (Formula I) where X can be lys or arg and y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys(col. 2, line 22) and Y=valine (col.2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). the preferred form of pro is also D (col. 2, line 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-4. Also see col. 2, lines 46-52, lines 59-61, col 3, lines 53-59, col. 4, line 59 to col. 5, line 3, and all the Examples and claims.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group, (3) the specific mention of Dlys-Dpro-Dval and (4) the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the primary reference clearly suggests the making and use of Dlys-Dpro-Dval (preferred embodiment).

Lipton discloses the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active that the unprotected form (col. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm2 to 10-10M/cm2 (abstract, col. 1, lines 5-42, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation include ointments and creams (col. 2, lines 50-55). Remington's is cited to show that formation of topical treatments and aerosols is well known in the art.

Therefore, in view of the suggestion of the primary reference to make and use Dlys-Dpro-Dval, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use Dlys-Dpro-Dval to treat pain. It also would have been obvious to one of ordinary skill in the art to use a protecting, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary and secondary reference are both derived from amino acids 11-13 of alpha MSH. It also would have been obvious to use of the tripeptides of the primary reference to treat inflammatory disorders of the skin and to

make formulations suitable for topical administration because according to Nordlund et al MSH is such to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of Il-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related). The combination of two or more known agents to treat a disease if within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

3-11, 16-19

14. Claims 1-3 and ~~5-15~~ are rejected under 35 U.S.C. 103(a) as being unpatentable over Oluyomi et al Eur. J. Pharm.. vol. 258 p. 131 (1994) in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Sciences, 16th Ed. (1980), CH 87 and 92.

Oluyomi et al disclose the use of K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (abstract, p. 134-135 and Tables 2-3). This reference also discloses that amino acids 193-195 of Il-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group and (3) the combination of another known anti-inflammatory agent with the tripeptides.

Lipton discloses the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer

stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active that the unprotected form (col. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm2 to 10-10M/cm2 (abstract, col. 1, lines 5-42, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation include ointments and creams (col. 2, lines 50-55). Remington's is cited to show that formation of topical treatments and aerosols is well known in the art.

In view of Lipton, It would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary and secondary reference are related. It also would have been obvious to use of the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is such to treat such disorders and the tripeptides of the primary reference are related to amino acids 11-13 of MSH. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

Conclusion

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Applicant is directed to the claims of Ferreira et al US 5580855.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is (703) 305-7866. The examiner can normally be reached on Monday-Thursday from 6:30am to 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703)308-2731. The FAX phone number for this Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sheela J. Huff
April 9, 1997

Sheela J. Huff
Patent Examiner
Group 1800